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Medical Research - The Global Landscape

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Thank you Chairman Gutmann and Committee Members.

It is a pleasure to address you today about the issues of the current and upcoming "Landscape of Medical Research in Developing Countries". I will address these issues from several perspectives. First, as a lifelong physician scientist and viral disease specialist who has been involved in the HIV epidemic from its inception and, for the last decade, I have been involved in the global effort to develop an HIV vaccine. Since 1998, I have led the NIAID supported HIV Vaccine Trials Network (HVTN). The HVTN has been created to speed the development of an effective HIV vaccine and it coordinates a global clinical trials program devoted to HIV vaccine research. The HVTN operates on four continents in 15 countries; currently nearly half of its research efforts are conducted in the developing world, specifically sub-Saharan Africa. Its efforts in this part of the world are scheduled to markedly increase.

I am sure all of you are aware that the developing world bears the greatest burden of HIV and hence, the development of novel HIV prevention strategies, including a vaccine, are necessary components of the global medical research agenda. Perhaps it is intuitive that many, if not most infectious diseases, should be studied at the global level. The worldwide transmission patterns of SARS, H1N1 influenza, MRSA, and penicillin resistant Streptococci have taught us that we are all increasingly interconnected. For communicable diseases, a global research platform is both efficient and necessary. To appreciate the contribution of global research, one only needs to pick up last week's New England Journal of Medicine to see an article from the Chinese Center for Disease Control, headed by Dr. Yu Wang, which reports on the safety of 90 million Chinese adults and children who received the H1N1 variant influenza vaccine. The article reported no increase in the frequency of Guillain-Barre syndrome; the side effect seen with a previous swine influenza vaccine in the 1970's. This article provides an important piece of information for future vaccination policy in the US and Europe.

I also want to talk about the landscape of global research for chronic diseases, especially cancer. On this topic I will speak from my perspective as the President of the Fred Hutchinson Cancer Research Center in Seattle, one of the original five National Cancer

Institute designated cancer centers created by President Richard Nixon in the early 1970's. The Hutchinson Center is where bone marrow transplantation was pioneered and is one of the largest free standing research centers in the nation.

Cancer is the world's leading cause of death. It may come as a surprise that the global burden of cancer in the developing world is even higher than in the developed world; especially for cancers that might be preventable and or effectively treated. We need to recognize this global burden of disease and initiate a plan to include cancer prevention, screening and treatment into the global research agenda.

The goal of medical research is to improve health, improve survival and quality of life. The attainment of these is a universal desire of humankind. The link between disease burden and economic and social development is clear; poor health indices are not only a marker of poor economic development, but also exert a causal relationship to poverty. Poor health equates to high maternal and infant mortality rates, poor childhood survival, decreased adult life expectancy, high burden of acute and chronic disease, and increasing poverty. Importantly, poor health influences access and the ability to take full advantage of schooling. This directly reduces the ability, both for an individual and for a country, to compete economically. If one is to have a global development strategy, then one needs a global health strategy and by definition, one needs to have a global medical research strategy. Improving health globally requires improving the research infrastructure locally for those working in health. Thus, perhaps the first obvious point for surveying the global landscape on medical research is the critical need to expand the types and amounts of ethical medical research in the developing world.

How do we create the tools and safeguards to implement a global medical research agenda? I will maintain that we already have several successful models. Perhaps the most developed is in the area of HIV prevention and therapy. For the last 5-7 years, most of the sentinel advances in HIV treatment and prevention have arisen from studies conducted in the developing world. These studies have been conducted at the highest ethical and investigative standards, and are shaping both the research and clinical practice agenda of citizens in both the developing world and industrialized countries.

I would like to highlight three successful insights in HIV prevention research that have come largely from trials conducted in the developing world, through successful and ethical collaboration with US and developing world scientists. The first major successful insight for developing an HIV vaccine emanated from a clinical trial performed in Thailand

by Dr. Nelson Michaels' group in collaboration with the Thai Ministry of Health; this trial transformed the HIV vaccine research and development landscape. Most recently, the iPrEx study demonstrated the concept that it is possible to reduce acquisition of HIV by taking antiviral drugs daily. This study has initiated a discussion about the use and licensure of such drugs in the United States. Of the 3,400 subjects enrolled in this HIV prevention trial, in men who have sex with men (MSM) only 10% of the participants were from the United States. Most of the clinical trial participants were from South America. Another study found that regimens found to be effective in the United States were expanded and adapted to improve the efficacy of regimens to prevent mother to child transmission of HIV in Africa. Yet another study conducted in South Africa found that starting antiretroviral treatment early in children reduced death by two-thirds. This study has changed international treatment guidelines and improved child health in our own country. Similarly, studies defining when to optimally start HIV therapy and how to minimize clinical failure are all now emanating from the large treatment programs initiated in Africa, Haiti, Peru and Brazil. All of these studies have led to improved care for HIV infected persons in the US and Europe.

One of the key features of the HIV research experience is that the studies are relevant to both the sponsors and funders in the developed world and especially to the participants in the countries in which the studies are being conducted. Conducting effective medical research globally requires establishing mutually beneficial partnerships with local researchers and research institutions. It is critical that local institutions and researchers are involved in conceiving the studies and that their input and innovations are valued. It is crucial that the research questions being raised are relevant to the community being studied. In addition, the community must be involved in defining the standard of care for the study. Within the HVTN, we operate on a simple principle that all of the research sites in any study are equal; we use the same ethical principles to guide our research regardless of where it is conducted. Our international investigators are involved in all our protocols, including ones conducted solely in the United States. International researchers occupy leadership positions in our research network. In addition, we are engaged in building in country infrastructure in low resource countries where our research is conducted, including building laboratory infrastructures to ensure that low resource settings are a part of the laboratory conduct of the research and specimens are not simply shipped out for developed country use.

Research partnerships need to be cultivated. My personal experience with such

partnerships is that having a freestanding independent medical research university, one that embraces the scientific and ethical principles of medical research and that is independent from the ruling political establishment, are critical features for implementing long range programs for medical research. These institutions are able to provide the human capital and the forums for training the diverse groups needed to perform research; especially those involved in establishing the ethical standards and reviewing research conduct. Cultivating such institutions and engaging in their development should be an important component of the overall strategic plan for biomedical research.

Partnerships also help insure that the research being conducted will be of benefit to the communities involved in that research. Do we value the input and innovation of Southern Hemisphere investigators? Again, the HIV field provides some useful examples. In sub-Saharan Africa three clinical trials of circumcision of heterosexual men were conducted to evaluate whether this procedure would reduce HIV acquisition; a strategy that dramatically and directly reduces a sub-Saharan African man's HIV risk (there is an indirect benefit to women on a population basis). Based upon these results, South Africa, Swaziland and a variety of other countries have initiated country-wide programs of adult male circumcision to reduce HIV acquisition. Such an approach for reducing HIV acquisition among certain populations in the US warrants such discussion.

Involvement of the community, especially the non-scientific community, is critical for successful research in the developing world. The community must be involved in the conceptualization of the research itself, not just in the IRB and informed consent process. Our organization has spent both energy and time in developing meaningful community engagement; not only for each clinical trial site, but also for the organization itself. Community members sit on all committees. They have equal voting rights and access to all documents. The HVTN supports the travel of community members to meetings where we develop our research protocols and to investigator forums. They are as integral to the research process as are the researchers themselves. The guiding philosophy is that a global research network should have fundamental working principles that are applicable for all its components. Cultural and linguistic differences must be acknowledged when communicating medical information, such as the pros and cons of genetic information. It can be challenging to explain the importance of host genetic susceptibilities to disease, genetic determinants of drug metabolism or the sequencing of a tumor to provide information on how to optimize therapy.

The process of informed consent must also be developed with community input. This

committee needs no discussion from me on this issue. Suffice it to say that true consent goes beyond signing a 12 page document and must incorporate many ways to reach the audience, whether through visual aids, DVDs, or street theater. Informed consent is about making sure there is understanding of the research and the research process. It is not only conveying information, but also assessing whether someone understands the research study. We are quite an individualistic culture; one that values autonomy and believes in the concept of individual privacy when making an informed consent decision. Yet in some cultures, community assent is critical, if not essential, for participation.

Another important component to the global landscape is equal access to therapy within the context of the trial. Are there differences in standards of care between sites involved in the same research study? While this is an issue that may vary between trials and locales, this is an issue that must be worked out among all the research partners. In the HIV prevention field, we needed to deal with access to antiretrovirals among persons who acquired HIV on our trials. HIV is not a complication of the trial itself, but rather an inevitable outcome of living in a country with a high incidence of HIV infection. We needed to examine: would antiretroviral therapy (ART) be available for all participants in Haiti as it were for persons in the US? To achieve this in many countries, we needed to provide a mechanism to make these life-prolonging drugs available to trial participants. This issue forced me as an investigator at the Hutchinson Center, as the organization coordinating the research, to start a nonprofit entity and raise funds for this endeavor. We use these funds to bridge access to ART until PEPFAR or Global Fund programs could be initiated in regions where we operated.

What is critical and yet may not reach the attention of the research establishment is the need to provide the personnel and funds to engage local communities in problem solving on the types of issues I have raised. I would urge the Commission to encourage that such funding be made routinely available, particularly for trials sponsored by private enterprises and foundations.

The commitment to action following the research is the area of most concern as one expands the global research agenda. Here is where the global burden of cancer may be used as a model for global research for the burden of chronic disease. The statistics on the global burden of cancer are staggering. Based on 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred worldwide in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world. Breast cancer is the most frequently diagnosed cancer and the leading

cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Lung cancer is the leading cancer site in males, accounting for 17% of the total new cancer cases and 23% of the total cancer deaths. Breast and cervical cancer are now the leading cause of cancer death among females in low resource settings. Cancer survival tends to be poorer in developing countries, most likely because of a combination of a late stage at diagnosis and limited access to timely and, for industrialized countries, standard treatment. In Uganda, we see mortality rates above 50% for children with Burkitt's lymphoma, a cancer with proven curative therapy. The rate is high because of lack of access to treatment. A substantial proportion of the worldwide burden of cancer could be prevented through the application of existing cancer control knowledge and by implementing programs for tobacco control and vaccination (for liver and cervical cancers in particular).

We at the Hutchinson Center and I personally am committed toward developing and extending cancer research programs into the developing world. We are currently involved with building and staffing a new Outpatient Research and Treatment Cancer Center in partnership with the Uganda Cancer Institute and the Ugandan Ministry of Health in Kampala. In addition, we have initiated a training program for Ugandan physicians in medical oncology. When we started, Uganda, a country with the population of Texas, had only one medical oncologist. We have now trained four and have three more in our current program. With help from the Fogarty Institute, recent funding from the National Cancer Institute, and in partnership with Makehere University in Kampala, we have now extended our training program to a wider scope of health professionals and administrative personnel required to perform a long range research program in both HIV- and non-HIV associated malignancies. We view this program as potentially transformative with respect to bringing novel therapies, including novel cost effective regimens, to medical oncology. While there are many details to such a program, the one that I want to highlight and which I think will be a common ground for discussion for the global research agenda for cancer and chronic disease, will be access to successful novel therapies, especially a novel therapeutic that has had extensive development costs.

Access to successful new therapies must be discussed at the time the research experience is initiated. While all aspects of such discussions need not be solved prior to conduct of the research, some common understandings must be acknowledged and their principles articulated on paper. There are models for this issue. Many global health

foundations, especially the Bill and Melinda Gates Foundation, have pioneered such discussions. They require global access agreements for all the research they fund. No such agreements are required by US Government standards or through commercially sponsored agreements. Realistically, these agreements are complex involving the sponsors, investigators and communities, health ministries and local regulatory agencies; a task that is daunting and often foreign to the investigators proposing the clinical trial. It is unlikely one set standard can be developed for every type of innovation and graded uptake of a novel therapy may be acceptable in many instances. At a minimum acknowledgement of the issue and providing the administrative framework for initiating these discussions should be in place.

In summary, new investigative areas will expand, especially in chronic diseases that burden both the developed and developing world. The increasing morbidity of diseases such as cancer, diabetes and heart disease will require the establishment of new global research networks and collaborations. Successful models of international collaboration do exist. These are based upon mutual beneficial long term partnerships; partnerships that involve funders, investigators from both the developed and developing world, and study participants with meaningful community engagement. These collaborations are, in my opinion, scalable. The most successful clinical trials are those that are conducted expediently, yet prudently to ensure that research is carried out at the highest standards and protect study participants from harm. Governments, especially the United States government which has led the world in global research partnerships, must drive this process.

Thank you for the opportunity to address the most important aspects of the global research enterprise: the protection and stewardship of study participants - without whom critical research advances would not be possible.